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Chapter 4

Autism in Children Connected with Gastrointestinal Symptoms

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Additional information is available at the end of the chapter

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Abstract

Autism in children has increased significantly over the last few years. Eating disorders and ailments of the gastrointestinal system are a common affliction among these children. The hypothesis linking the autism spectrum disorder (ASD) and the digestive system with its bacterial microflora based on the concept of the gut-brain axis become very interesting and credible. This axis is a two-way communication between the central nervous system (CNS) and gut innervation. Mechanisms of this dependency include effects of neurological, immunological, and hormonal mediators. Among patients with ASD, mucosal permeability is frequently diagnosed, which may be caused by chronic inflammation. Such inflammation can damage cells of the intestinal membrane. Children with ASD also have a different composition of intestinal and gastric flora compared to healthy ones. Different types of environmental and situational stressors may contribute to the occurrence of gastrointestinal disorders such as irritable bowel syndrome, enteritis, as well as increase intestinal permeability and change their bacterial flora. The chapter presents eating disorders and nutritional deficiencies in children with ASD and shows how nutrition during pregnancy can affect ASD symptoms and how to reduce the severity of ASD symptoms through carefully selected nutritional interventions and supplementation.

Keywords: autism, eating, gut-brain axis, nutrition, gastrointestinal symptoms

1. Introduction

One of the most common symptoms of autism spectrum disorder (ASD) affecting children is problems related with nutrition and eating habits (46–89%) compared to healthy children (25%) [1]. Children with ASD usually prefer consuming products of one type and one color,

with a specific texture and smell, or having the same or similar packaging. They also refuse to try new foods and have specific nutritional behaviors, for example, they eat in a ritualistic way [2, 3]. Children with ASD have also problems with their digestive system, such as constipation, diarrhea, bloating, esophagitis, and reflux [4]. Due to the fact that gastrointestinal disorders may affect the incidence and severity of other symptoms in children with ASD, adequate nutrition should play an important role in treatment of mental symptoms. This can improve their life comfort and overall health.

In order to explain the etiology of autism, many hypotheses have been created that combine the occurrence of this disorder with genetic determinants, environmental influences, autoimmunity, viral infections, and drugs. One theory links the ASD symptoms with the gastrointestinal disorders and the composition of the intestinal flora [5]. It is based on the concept of the gut-brain axis, that is, the interaction between the gastrointestinal tract and the nervous system. This axis is a two-way communication between the central nervous system (CNS) and the gastrointestinal tract controlled with autonomic nervous system (with sympathetic and parasympathetic nerves). Mechanisms of this association include the action of neurological, immunological, and hormonal mediators [5, 6]. The increased permeability of the intestinal membrane, which commonly occurs in autistic children, can lead to excessive penetration of the blood exogenous peptides incompletely hydrolysed due to impaired digestion of casein and glutamine in the intestinal lumen. These peptides are transported to the brain, where they pass through the blood-brain barrier and as neuro- and immunoactive substances interfere with the neurological mechanisms of brain development [3, 7]. The biological activity of these compounds comes from their structural similarity to the endogenous opioid peptides [8]. The intestinal microflora can also affect the functioning of the CNS through the ability to synthesize identical or similar neuroactive molecules such as, inter alia, acetylcholine, catecholamine, histamine, or melatonin. On the other hand, the composition of intestinal bacterial flora may also depend on the level of stress or intensity of emotions; thus the digestive and nervous systems interact with each other [7].

2. Eating disorders and gastrointestinal complaints

Parents of children with ASD most frequently observe the selectivity of food and a very narrow range of consumer products [3, 9]. Eating disorders in children with ASD can be divided into the three following categories: (1) refusing to eat, (2) limited range of food consumed, and (3) frequent consumption of one product [10]. It was shown that children with ASD choose food based on its texture (69%), occurrence (55%), taste (45%), smell (36%), and temperature (22%). There was also a reluctance to try new food products in 69% of respondents [11].

Children with ASD aged 2–12 years are characterized by poorer skills of independent eating, more frequent occurrence of avoidance, and neophobia of food in comparison to the healthy peers [3]. These children also prefer energy-rich products such as hotdogs, peanut butter, cakes, fries, and pasta, while they eat a few vegetables and fresh fruit [12, 13]. It was also found that obesity in children with ASD can occur more likely than in healthy children [3].

The prevalence of eating disorders such as selectivity and refusal to eat reaches almost 90% in children with ASD [1, 2, 14]. A UK study found that 59% of children who had ASDs were eating less than 20 different foods [9].

The most common gastrointestinal complaints are constipation, diarrhea, abdominal pain, and reflux. It has been also found that they may suffer gastric acid hypochlorhydria, intestinal motility disorders, decreased activity of disaccharidases, and primarily lactase in intestinal juice [4, 8]. It has been also observed that 70% of children with ASD suffer from gastrointestinal disorders, where in healthy children this frequency was only 28% [5, 15]. In accordance with the other studies, gastrointestinal complaints are five times more frequent in children with ASD; abdominal pain occurs twice as often; and constipation and diarrhea are four times more often than in healthy controls [16]. However, the higher incidence of gastrointestinal complaints in children with ASD is not clearly stated, as not all studies show such dependence [3, 15]. It is often also suggested that gastrointestinal symptoms may be related to the medication being taken and the side effects they may cause [3].

Studies in which intestinal biopsy was performed among children with ASD suffering from food disorders showed a deficiency of disaccharidases and hexose transporters. This may indicate that the digestive system carries incorrect digestion of carbohydrates and their transport through enterocytes. Decreased digestion and absorption of these compounds may result in the accumulation of sugars in the intestinal lumen, and this can lead to the occurrence of osmotic diarrhea and bloating [5].

People suffering from ASD frequently have increased intestinal mucosal permeability, which may be due to their chronic inflammation. One of the studies carried out among children with ASD showed a significant increase in CD3 + and CD8 + lymphocytes in the intestinal epithelium and increased expression of proinflammatory cytokines in their mucosa. Elevated levels of cytokines were associated with the occurrence of behavioral and communication disorders [5].

Children with ASD can be characterized with a different composition of the bacterial flora of the stomach and intestines. Studies have shown in children with ASD a reduced amount of *Bifidobacteria* and more frequent occurrence of *Bacteroides vulgatus* and *Desulfovibrio* than in healthy ones [5, 7]. Higher amounts of *Clostridia* were found in their stool, which may be associated with a more frequent occurrence of problems from the digestive system [5].

3. Nutritional deficiencies

Due to the selectivity of food and a little varied diet, the intake of vitamins and minerals in children with ASD may be insufficient and lead to malnutrition. This applies in particular to vitamins A, D, K, and B12 as well as calcium and zinc [3, 9, 10, 17]. Research in which nutritional diaries were used, covering 3 days in the group of children aged 8–11 years, showed that insufficient intake of vitamin D, calcium, and vitamin A occurred more frequently in children with ASD than in the group of healthy ones. There was also an increase in protein

intake in children with ASD, higher than the recommended norm by 111%. Children with ASD were also characterized by a higher intake of vitamin B6 and vitamin E [3].

It was found that in people with ASD, the intake of vitamin E and B6 is higher than in healthy people, while the intake of iron, calcium, and vitamin D is significantly lower. It was also found that children characterized by food selectivity are more exposed to calcium, zinc, and vitamin D deficiency. Examining the amount of nutrients consumed in children with ASD with a narrow range of eaten products, they confirmed an increased risk of deficiency not only of vitamin D, calcium, and zinc but also vitamin B12 compared to healthy ones [17, 18]. Based on a study in which a 3-day nutritional interview was used, it was shown that in the group of children with ASD aged 4–8 years, the intake of calories and protein is too low and the intake of carbohydrates higher than recommended. Insufficient intake of vitamin D was diagnosed in 87% of children under the age of 4, in 89% of children between 4 and 8 years of age, and in 79% of children between 9 and 11 years of age [19]. Studies indicate a higher incidence of folic acid; vitamins B6, A, C; zinc; and calcium deficiency in children with ASD than in healthy ones [20]. Other studies show that the intake of protein in the children with ASD exceeded the norm by more than 171%, and the supply of animal protein was exceeded by 200%. The excessive consumption of sodium, phosphorus, magnesium, and vitamins A, C, and B and insufficient supply in the diet of vitamin D, calcium, iron, potassium, fiber, and cholesterol were also indicated [8]. However, the majority of people with ASD are characterized by excessive intake of vitamin C and low carotenoid intake [19, 21]. In another group of children with ASD examined for nutritional deficiencies, insufficient calcium intake and excessive supply of vitamin B6 and E were found. Too little intake of iron, calcium, vitamin D, and fiber was found in both children with ASD and in the group of children developing properly [9].

4. Nutrition and nutritional behavior during pregnancy

The diet of a pregnant woman affects the growth and development of the fetus, including the maturation of his brain. It can therefore be assumed that there is a probability of dependence between maternal nutrition and an increased risk of ASD in a child. It has been shown that the risk of ASD is about 40% lower among those children whose mothers took folic acid before conception 6 weeks and 6 weeks after conception. Women who had healthy children consumed 123.9 ± 46.4 μg more folic acid than mothers of children with ASD. Schmidt et al. found lower intake of folic acid in the first month of pregnancy in women who had children with ASD than mothers of healthy children. The relationship between the increase in folate intake and the decrease in the risk of ASD was demonstrated [22]. There was also a higher intake of polyunsaturated fatty acids (PUFA), before and during pregnancy, among women whose children developed normally than mothers of children with ASD. According to the study, women whose intake of omega-3 acids in the study group was the lowest had a 53% higher risk of giving birth to a child who had ASD than women with a middle range of consumption of these acids [23]. In other studies, there was no evidence of a decrease in the risk of ASD with an increase in the intake of omega-3 acids above the norm, but it has been proven that the risk increases with a very low intake of these acids [24]. It may also be important for pregnant

mothers to eat fish, which is a rich source of unsaturated fatty acids and vitamin D. However, no study has linked the amount of fish consumed by pregnant women to the occurrence of ASD in their children. It was suggested that a small intake of vitamin D, by a pregnant woman, may be a risk of ASD in a child, but this relationship was not confirmed by any study [22].

Obesity of the mother and eating a diet full of fat during pregnancy can also increase the risk of ASD in the child. The increase in the prevalence of ASD was associated with a higher rate of obesity [25]. The offspring of obese women are more exposed to the appearance of behavioral disorders such as depression, anxiety, ADHD, and ASD. It is related to the influence on the fetal development of factors related to maternal obesity, among others, hyperlipidemia, hyperglycemia, and insulin resistance [25]. Compared to children of women with normal body mass, in obese children (II and III classes) ASD was diagnosed more frequently [26]. A relationship between the occurrence of ASD and excessive weight gain in women during pregnancy has been demonstrated. There was also an increased risk of developing ASD in children whose mothers were obese prior to pregnancy [26]. One of the theories explaining the association of obesity in children with ASD is the occurrence of higher levels of leptin. This causes placental dysfunctions, which may disrupt the normal, neurological development of the child [25]. People with autism have more leptin in plasma than healthy subjects [11]. Obesity is considered to be an inflammatory disease; it causes an increase in inflammatory cytokines in the body that reach many organs, including the brain. Therefore, excessive body weight and maternal diabetes can activate the inflammatory response in the placenta [25]. Diet high in fat in pregnant women stimulates inflammatory cytokines, including interleukin (IL-4, IL-5) and monocyte chemoattractant protein-1 (MCP-1). These cytokines have been associated with the occurrence of ASD. In addition, these compounds transmitted by obese or mothers with diabetes to the fetus can initiate physiological and behavioral responses observed in children with ASD whose mothers during pregnancy have developed infections [25].

5. Nutritional interventions

A gluten-free diet relies on elimination from diet products containing wheat, oats, barley, and rye (as well as flour, bread, pasta, cakes, and other products made from these cereals). The casein-free diet (dairy free diet) relies on avoidance of the consumption of milk including breast milk, dairy products, yogurts, cheese, butter, cream, ice cream, and others [27]. Gluten-free and casein-free (GFCF) diets are one of the first nutritional interventions offered to patients with ASD. Many parents have reported improvements in maintaining eye contact and talking to children with ASD who have been on this diet [28]. In the study describing the study conducted on a group of 149 children diagnosed with ASD, it was found that after the introduction of the GFCF diet and its use for 3 months, a significant improvement in 81% of children was observed. However, the authors questioned the significance of the results of this study, because the conclusions on the health status of children and its improvement were drawn by their parents, aware of the conducted nutritional intervention [28]. A blind experiment was carried out among children with ASD regarding the use of the GFCF diet. In both control and research groups, there were 10 children with ASD. In one group, an intervention

was introduced relying on elimination of gluten- and casein-containing products from the diet, while the other group continued their previous diet. Observations were made before the beginning of a nutritional intervention and after 1 year from the beginning of its implementation. The tests that were used were based on, inter alia, nonverbal techniques. There was a statistically significant improvement in the ability to learn in a group of children using a diet with the elimination of gluten and casein [14, 20]. In another paper, in one of their presented examples, the GFCF diet began to bear effects after only 2.5 months of its use. An improvement in social communication and in emotional reactivity was recorded [29]. Antibodies of IgG, IgM, and IgA against gliadin, casein, basic myelin protein, maize, eggs, and soy in 50 children with ASD were measured. Analysis of blood samples showed that a large number of children produced antibodies against casein and gliadin. In addition, it was found that these proteins bind to lymphocytes and CD26 enzymes, which can cause inflammation and activate the immune system response [30]. Behavioral changes in ASD patients may result from abnormal activation of the opioid system due to excess receptor antagonists in the brain. It was found that gluten and casein are the source of compounds characterized with the activity of opioid peptides [31]. Fifteen children with ASD who did not show any food intolerance took part in another study. They were divided into two groups and blinded. For 12 weeks, one group was given a diet with the elimination of gluten and casein and the other a diet enriched with these substances. After this time, each group went on an alternative diet for the next 12 weeks. The carers or parents of the examined children were not aware of the kind of food their child was receiving. There was no difference in the behavior and development of the child in any group [15]. The influence of a diet containing gluten and casein on the behavior and complaints from the digestive system in children with ASD, which until then used diet with the elimination of these substances, was investigated. The study was randomized, double blind, and controlled; the experimental group consisted of 38 people and the control group of 36 people. According to the authors' hypothesis, the introduction of autistic gluten and casein into children's nutrition was to cause deterioration of their behavior and gastrointestinal complaints. Nutrition interventions were carried out for a week. There were no differences in the health status between the test and control groups. It was suggested that the result of the study could be affected with the short intervention time [32]. Many studies on the GFCF diet focus on the safety of the intervention [31]. In various studies, no differences were observed in the nutrition of children with ASD using the GFCF diet compared to children on the standard diet. However, a significant reduction in the concentration of amino acids was observed, including tryptophan in children using GFCF diets. In addition, patients using a gluten-free diet were found to consume larger amounts of proteins and fats but smaller amounts of carbohydrates, fiber, calcium, and iron [31]. Therefore, it warns against the risk of insufficient supply of micro- and macroelements while using the GFCF diet [29, 32]. The casein-free diet can cause calcium deficiencies. In addition, slower bone development in children using such nutritional intervention was also reported in comparison with children without any dietary restrictions. It was shown that patients with ASD on a non-denaturing diet had lower bone density than the control group. Lower vitamin D intake is also seen in such patients [11, 29, 32].

Another nutritional intervention in children with ASD is a ketogenic diet, which is characterized by an increased fat content, adequate to the amount of protein needed and insufficient for metabolism the amount of carbohydrates, which leads to the body's use of lipids as the

main source of energy. In the original ketogenic diet, the ratio of calories from fat to calories from carbohydrates and proteins was 4:1 (the proportions were 80% of lipids, 15% of proteins, and 5% of carbohydrates). With a standard diet, fatty acids are catabolized to acetyl-coenzyme A (CoA) in the oxidation beta reaction and then oxidized to CO_2 and H_2O in the Krebs cycle. However, when the amount of fatty acids is too high and exceeds the ability of the Krebs cycle to metabolize CoA (e.g., low carbohydrate or protein diets), in the acetyl-coenzyme A, the liver is converted to ketone bodies (acetoacetate and D-beta-hydroxybutyrate). Ketone bodies produce a similar amount of energy as proteins and carbohydrates; they can also cross the blood-brain barrier, so they can be used by brain cells as a source of energy [33]. Ketogenic diet is an alternative or supportive therapy for patients with drug-resistant epilepsy. It was found that in patients using these diets, it was easier to control epileptic seizures as well as their frequency. The ketogenic diet is also used in other diseases such as Alzheimer's disease, Parkinson's disease, migraine, and depression [33, 34]. The ketogenic diet is also used as an option to suppress symptoms accompanying ASD [35]. The study evaluated the effectiveness of the ketogenic diet in a group of 30 children with ASD. Children were evaluated before and after dietary intervention using the Childhood Autism Rating Scale (CARS) scale. It was found that a significant improvement occurred in two patients, the average in eight patients, and a slight improvement in eight patients. Nutritional intervention, in addition to the introduction of a ketogenic diet, also consists of supplementation of vitamins and minerals dosed depending on the age of the subjects. According to the authors, the research on the effectiveness of autistic treatment by ketogenic diet should be extended and continued. The studies showed that in patients who were characterized with a higher CARS score, the improvement in the results of ketogenic diet treatment was lower than in patients with moderate or light ASD [35]. Because the characteristic composition of the ketogenic diet is quite distasteful, often patients decide to interrupt this diet intervention and return to the previous method of nutrition. This diet may additionally lead to nutritional deficiencies [35]. It also has numerous side effects including weight loss, growth inhibition, fatigue, drowsiness, changes in appetite, constipation, diarrhea, nausea, and vomiting [33]. In one of the studies in which the impact of the ketogenic diet on the symptoms of ASD was analyzed, constipation or diarrhea appeared in 12% of children with ASD [35]. Due to the limited number of research results on humans and on animal models stating the reduction in the frequency of behavioral disorders, after using the ketogenic diet, it cannot be unambiguously determined its effectiveness in children with ASD.

6. Supplementation

Vitamins and minerals play an important role for human health, because they have numerous functions in the body, including enzyme cofactors for many reactions. In particular, attention is paid to the insufficient supply of vitamins and minerals in the diet, as one of the causes leading to many health problems in children, for example, anemia, hypothyroidism, or rickets. Recently, researchers have focused on the relationship between metabolic disorders and developmental disorders, including lack of concentration, learning disabilities, and intellectual development [21]. Children with ASD due to diets, often restrictive, may be exposed to nutrient deficiencies. Dietary supplements are one of the most frequently recommended

nutritional interventions for children with ASD, recommended by 49% of physicians [21]. Other studies suggest that 66% of people with ASD are taking supplements—most frequently probiotics, omega-3, vitamin B6, and melatonin [36].

Probiotics are defined as living, nonpathological microorganisms, which have a beneficial effect on the human body, when of course administered in the right dose. They consist mainly of lactic acid producing bacteria, *Lactococci* and *Bifidobacterium* or yeast, that is, *Saccharomyces boulardii* [36]. Probiotics have a beneficial effect especially in gastrointestinal problems such as infectious diarrhea, inflammatory bowel disease, or hypersensitivity syndrome of the large intestine. Their activity in shaping the host's immune system has also been proved [36]. They can also be effective in the treatment of inflammatory diseases of the gastrointestinal tract and affect the function and permeability of the intestinal epithelium. An important role is also played in restoration of the intestinal microbial balance [37]. It was found that probiotics can be effective in the treatment of children with ASD due to their health-promoting effects on the gastrointestinal tract and the entire body [36]. It has been pointed out that the use of probiotics may help in restoring the proper intestinal microflora and thus eliminate diarrhea and constipation, which are a common problem in people with autism [38]. It was also pointed out that this supplement may play a role in maintaining the continuity of the gut mucosa, activating the immune system and preventing inflammation [39]. A relationship was found between the severity of ASD and gastrointestinal disorders. It can therefore be considered that probiotics contributing to the improvement of this system may also positively affect the behavior of children with ASD. Almost 20% of physicians are encouraged to take probiotics in children with ASD, and 60% of physicians recommend continuing to use probiotics, if parents have decided to apply such supplementation [36]. It is also important to mention that although the US Food and Drug Administration (FDA) considered probiotics to be safe for health, so far no research has been conducted that would address the long-term effects of their supplementation.

In the studies carried out so far, 50% of children and adults with ASD have shown positive effects of vitamin B6 supplementation [40]. According to studies, children with ASD who do not take any supplements are characterized with a higher level of vitamin B6 in plasma than the control group subjects. There are more studies that confirm this phenomenon [40]. One of the explanations is the lower activity of vitamin B6 in people with ASD. It was also found that pyridoxal kinase—an enzyme responsible for the conversion of pyridoxal to the active form of vitamin B6 (PLP, pyridoxal phosphate), in this group of people—is also characterized with a slowed effect [39, 41]. This activity can be lowered by up to 40% compared to people developing properly. PLP is an essential component for the synthesis of mitochondrial components, among others, heme and coenzyme Q10. It has also been shown that this compound protects neurons from excessive oxidative stress by increasing the production of ATP and the use of excess glutamate [42]. People with ASD may notice an improvement in health during supplementation with a high dosage of vitamin B6, which will lead to increased energy production, decreased excitotoxicity, and reduction of oxidative stress. Some of the parents, when using such dietary intervention, observe in children with ASD improvement in the areas of attention, communication, learning, or maintaining eye contact [39, 40]. Often when supplementing vitamin B6, it is also recommended to take magnesium for the purpose of preventing its deficiency and reduction of the level of hyperactivity. In addition, this element

blocks excessive irritation of excitotoxic receptors in the brain by means of calcium channel modeling [42]. Supplementation of these two nutrients led to improved behavior in children with ASD [36, 39]. In one of the studies in which the double-blind method was used, it was found that in children supplementing magnesium and vitamin B6, behavioral improvement was noted, while in groups in which only magnesium or vitamin B6 was administered, this improvement was not observed [43]. One of the 9-year-old boys with ASD, who was prescribed supplements with B6, magnesium, and additionally vitamin B12, decreased sleep problems and improved behavior [43]. At present, it is not known what the possible side effects of taking vitamin B6 may be. Older studies show that long-term supplementation of this nutrient may increase the risk of developing peripheral neuropathy [44].

Omega 3 acids belong to the group of polyunsaturated fatty acids (PUFA). They include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). A lot of research confirms that EPA and DHA are important for both the structure and functioning of the brain. Supplementation of these acids is recommended for the treatment of disorders of the nervous system, such as schizophrenia or ADHD [43, 44]. The anti-inflammatory effect of PUFA has also been proven, which may also include a reduction in the number of proinflammatory factors in the body such as Il-6, Il-10, and TNF alpha. The rich sources of EPA and DHA are fish products and seafood while ALA plant products [45]. There are many studies on the role of deficiency of omega 3 in children with ASD. Lower levels of omega 3 were observed in children with ASD compared to the healthy ones. According to the research, the difference in the level of these acids in the research and control group reaches about 10% and nearly 29% of children with ASD supplementing omega 3 [44, 45]. For 6 weeks, 1.5 grams of fish oil was given to 13 children with ASD aged 5–17 years. An improvement in the occurrence of hyperactivity in these children was sought [43, 44]. Similar results were obtained in studies where the supplementation was used for 12 weeks in patients with ASD aged 3–8 years [45]. Thirty children with ASD for 3 months were supplemented with omega 3, omega 6, and vitamin E. An improvement was noted in 20 children, which was confirmed by the Childhood Autism Rating Scale [46]. Omega 3 fatty acid supplements are generally considered safe but their consumption in larger quantities may increase the risk of bleeding and mercury poisoning, which may be contaminated with fish products, which are a good source of fatty acids.

Vitamin D is a fat-soluble vitamin; it occurs in three forms: D1 (calciferol), D2 (ergocalciferol), and D3 (cholecalciferol). The main source of Vitamin D is skin synthesis and food products (marine fish, fish oils, and to a lesser extent meat and dairy products, in which it occurs as a cholecalciferol). For a long time, vitamin D was only known for its positive effect on the skeletal system and mineral metabolism. For several years, numerous studies have been conducted and provided information on other functions of vitamin D, previously unknown to anti-inflammatory effect, protection of mitochondria against oxidation, elevation of glutathione levels, and influence on at least five proteins that regulate DNA repair, increase in seizure threshold, or increase regulatory T lymphocytes. One of the most frequently studied areas in relation to the effects of this vitamin is brain development and mental disorders. It has also been proven that vitamin D can have a positive effect on the treatment of certain autoimmune diseases, for example, multiple sclerosis, because the receptors of this vitamin have been found in lymphocytes and dendritic cells. The research into the possible impact of vitamin D deficiency on the incidence and course of autism

has also been intensively developed. Low levels of cholecalciferol in the body and ASD have many similarities with regard to their etiopathogenesis. ASD findings indicate that this disease is more common in urban areas, in a climate with less sunlight, and in areas with higher environmental pollution, which also coincides with the etiology of vitamin D deficiency [47]. A hypothesis was proposed in which the deficiency of vitamin D, both in mothers during pregnancy and in children, is considered as an environmental risk factor for ASD. As a justification, the role of this vitamin in the maintenance of homeostasis of the brain, embryogenesis, and development of the nervous system or modulation of the immune system is given. It was also noticed that the children of women who used antiepileptic drugs with negative effects on the metabolism of vitamin D in the body were more likely to have a deficiency of cholecalciferol and ASD [48]. Vitamin D may also play a role in reducing DNA damage, acting as an intermediary in its repair, and genetic mutations resulting from DNA damage are also involved in the pathogenesis of ASD. T-cell dysfunction in patients with ASD, which is also influenced by vitamin D, is also revealed. Another theory of ASD etiogenesis is insufficient supply of adequate amount of vitamin D during the first 12–24 months of life [49]. It has been shown that children with ASD have a lower level of calcidiol and calcitriol in the body than the control group, consisting of healthy children [50]. The level of vitamin D was compared in the group of 50 children with ASD with a control group including 30 healthy children. Children with ASD had a lower level of vitamin D than the control group, and as many as 48% of them had deficits in vitamin D, although it was found that the amount of time spent in the sun was similar in both groups [49]. One of the studies attempted to reduce the symptoms of ASD in children by supplementing vitamin D. Sixty-seven subjects were given 5000 IU of vitamin D per day. Improvements in behavior such as reduced irritability, drowsiness, social withdrawal, and hyperactivity were observed [51]. One of clinical cases included a 32-month-old child diagnosed with ASD, characterized with severe symptoms including impaired communication; reluctance to social interactions; lack of reaction to other people, to commands from their parents, when their name are called, and to physical contact; avoidance of the eye; and delayed language and communication development. The child also had tantrums. The tomographic examination did not show any changes in the brain, and serum and urine tests did not reveal any metabolic deviations. Diagnostics in the direction of autism was carried out using scales, for example, Autism Behavior Checklist and Childhood Autism Rating Scale. The patient also had low levels of vitamin D at 12.5 ng/ml. It was decided to subject the child to supplementation with vitamin D, intramuscularly at 150,000 IU once a month and orally 400 IU per day. After 2 months, parents noticed a significant improvement in the child's behavior. The child began to respond to his name, let his parents cuddle, and play with toys. Laboratory tests showed an increase in the concentration of vitamin D to 81.2 ng/ml. The results and assessment made with the aforementioned scales have also improved. This example may suggest that vitamin D plays a large role in improving the basic symptoms of ASD; however, the observations made in this clinical case cannot be transferred to all patients with ASD. It is worth emphasizing, however, that research in this direction should be broadened and continued [52].

7. Conclusion

One of the most common problems in ASD is eating disorders and gastrointestinal complaints. Nutritional problems occur 2–3 times more frequently in children with ASD than

in healthy children [1]. The most common symptoms from the digestive system are constipation, diarrhea, bloating, and reflux. Almost 70% of autistic children suffer from it [2, 53]. Given these reports, the hypothesis combining the symptoms of autism with the functioning of the digestive system and its bacterial microflora based on the concept of the gut-brain axis becomes very interesting and credible [54–57]. Different types of environmental and situational stressors may contribute to the occurrence of gastrointestinal disorders such as irritable bowel syndrome, enteritis, as well as increase intestinal permeability and change their bacterial flora [58–66]. Differences were found in intestinal microbiome in children with ASD compared to healthy ones based on the analysis of metabolic products and composition of fecal flora [59, 67]. Gut microbiota-mediated metabolites, such as short-chain fatty acids (SCFAs) and free amino acid (FAA) concentrations, are significantly higher in children with ASD than healthy ones [68, 69]. The SCFAs are mainly produced by *Clostridia*, *Bacteroidetes*, and *Desulfovibrio*, and they can cause symptoms similar to ASD [70]. Fecal samples from children with ASD compared to healthy ones have higher levels of the *Clostridium histolyticum* that can produce neurotoxins [71]. Children with ASD have less differentiation and lower levels of *Bifidobacterium*, *Coprococcus*, *Firmicutes*, *Prevotella*, and *Veillonellaceae* and higher levels of *Bacteroidetes*, *Caloramator Clostridium*, *Desulfovibrio*, *Lactobacillus*, and *Sarcina* [59, 72].

One of the most interesting and surprising results in our own research is that children with ASD were characterized by greater intake of offal and red meat than healthy children. As many as 32% of children with ASD eat red meat several times a week. On the other hand, offal is consumed 1–3 times a month by 25% of examined children with ASD [73]. Offal and red meat are a rich source of iron. Perhaps this mineral ingredient can cause frequent consumption of the abovementioned products by children with ASD. Iron plays an important role in the development of cognitive, motor, and behavioral functions. It is also an important mineral component which, as a component of some enzymes, is involved in synthesizing neurotransmitters. Iron deficiency in children with ASD is very common. It has been shown that 24.1% of examined children with ASD have reduced iron levels and 15.5% suffer from anemia due to deficiency. The reason for such frequent iron deficiencies and hence the low level of ferritin present in autism is unknown until now. One of the hypotheses concerns the symptoms of the digestive system and the possible absorption disorders, which makes the iron from food less absorbed. It was found that this hypothesis is erroneous because in their studies, supplementation of this element in children with ASD caused an increase in the level of ferritin and iron, which excludes the problem of absorption deficits [74].

Due to the large interest in this topic, many papers have been made to assess the nutrient intake of children with ASD. The results of these studies often differ from each other, which probably results from the preferences of nutrition of children with ASD. On the basis of numerous studies, it can be concluded that in people with ASD, an inadequate intake of nutrients is more common. These deficiencies may not only lead to an increase in ASD symptoms but may also initiate the development of diet-related diseases. Many pediatricians recommend their patients with ASD to check the level of calcium, iron, and vitamins in the blood and prescribe multivitamin preparations or probiotics [21, 36, 41, 55, 64].

Several studies have reported that the most common diet products chosen by children with ASD are fast food products, that is, French fries, hotdogs, hamburgers, as well as candies, sweets, and products containing preservatives [12, 13]. In the conducted research, 27% of

parents answered that the child does not prefer to consume any type of products, and 25% that the child most eats sweets. It is interesting that fast food products, sweets, and other products characterized by the content of artificial food additives are eaten much more often in the group of healthy children than people suffering from autism. Artificial food additives such as preservatives, dyes, flavor enhancers, and sweets can cause hyperactivity in some children as well as impede concentration or learning opportunities. These symptoms are characteristic of such disorders as autism or ADHD. Studies have been carried out in which a change in diet in people with ASD led to an improvement in the functioning of the gastrointestinal tract and to the improvement of the psychological and neurological symptoms of this disorder [55, 58, 63]. This indicates an important role of bacterial microflora, which is based on the concept of the gut-brain axis of etiopathogenesis and ASD therapy in children. The relationship between the digestive and nervous systems is closely related; therefore diet therapy should be an important element in the treatment of autism.

Conflict of interest

I confirm there are no conflicts of interest. The funding organization played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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